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Pharmaceutical Co-crystals - Are we there yet?

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In the pharmaceutical arena it is agreed that co-crystals form a vital part of the solid-state toolbox, allowing the progression of novel compounds through the development pathway to patients and improving properties in older medicines. Sadly though, few co-crystals have made it to the market in the form of a new licensed product. This displays a disconnect between research effort and end product. For some time now it has been possible to determine the formation of co-crystals, by a variety of screening and analytical means; although it is recognised that there will always be phases that sit in the 'greyer' area of the salt-co-crystal continuum. It is also possible, with limitations, to predict the formation of co-crystals *in-silico* via energetic and structural considerations. So what are the major hurdles and missing links, and what are the key structural properties we need to study to improve the success rate? This highlight hopes to address these.

Introduction

The term pharmaceutical co-crystal has been with us in earnest for the last decade.[1] Interest in these solid phases stems from their potential to significantly alter the physical properties of an active pharmaceutical ingredient (API). There has been significant progress in this area with improvements achieved in an APIs properties in; dissolution rate, exposure, chemical stability, hydration behaviour and tableting performance to name but a few.[2-6] The potential for API property improvement hasn't been borne out in terms of new molecules entering the market as formulated co-crystals. There are a number of APIs on the market which on close inspection are indeed formulated as co-crystals, not the salts they were originally purported to be; these include Depakote and caffeine citrate.[7] Overall the number of new drug applications (NDAs) for co-crystals remains low however. Why is this and what are the missing pieces that will mean functional co-crystals can be more widely applied in the pharmaceutical context?

Definition and Regulation

Although the subject of numerous and vigorous debate, generally accepted literature definitions of co-crystals within the broader context now exist.[8] The naming of pharmaceutical co-crystals however has a significant bearing on their final function i.e. use in patients, regardless of the functional advantage served by any phase itself. This is because of the regulatory landscape which must be navigated for an API to make it onto the market and then into patients, quite rightly as these agencies ensure drugs reach patients in a safe and reproducible fashion.
The most recent, and all-encompassing, definition of a pharmaceutical co-crystal is as follows:

'*Co-crystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.*'

This definition came from the published outcome of the Indo–U.S. bilateral meeting.[9] This meeting and its subsequent

outcomes were motivated by publication of the draft FDA guidance on co-crystals. This regulatory guidance, now progressed from draft status un-changed[10], has taken the standpoint that co-crystals are;

'Solids that are crystalline materials composed of two or more molecules in the same crystal lattice.'

In practical terms this means that US FDA has elected to classify co-crystals within their framework as dissociable "API–excipient" molecular complexes, where the co-former is the excipient. This is converse to salts where a new salt is considered as a new drug entity. The FDA has taken the position that a co-crystal may be treated as a drug product intermediate rather than the drug substance. The main advantage of this decision is that it retains a less cluttered regulatory landscape and it offers the potential of an abbreviated new drug application (ANDA), rather than the full NDA needed for salts. This decision is potentially inhibitory to co-crystal development in novel APIs and a dual edged sword for older molecules. For the generics industry although it offers a faster route to market approval via the ANDA vs. a novel salt it also requires greater screening effort to be undertaken than for salts, due to the greater number of potential second entities (co-formers) associated with discovering a functional co-crystal. The number of second entities for use as co-formers is potentially unlimited, but as human safety testing is required for formulation additives in the pharmaceutical context it is normally restrained to the Everything Added to Food in the US (EAFUS) or Generally Regarded as Safe (GRAS) list.[11] The EAFUS list currently holds around 4000 entries of which a large proportion are present on the GRAS list and around 2000 have some toxicity data. The FDA also have an additional list which is compiled by the Select Committee on GRAS Substances (SCOGS), this list is maintained to analyse the health impact, and potential future risks from increases in dose, of compounds on the GRAS list. This list contains a more modest 332 compounds (260 compounds in category 1, 72 in category 2) which are known to be completely safe at current levels and may pose no/limited risk if increased in dose. Sadly few of these compounds are compatible with co-crystal design strategies, so the list remains long. The number of entities needed to screen is not however so inhibitory as to override the benefits conferred by the option provided by the FDA of the ANDA route; screening strategies will be discussed in the following section.

The regulatory delays that can be envisaged from the FDAs decision on co-crystal classification will be in those co-crystals systems for which definition is not immediately obvious, due to ambiguous charge state of one or more components within the lattice and the subsequent position on the salt-co-crystal continuum.[12] Partial charge on the API or co-former, temperature dependant proton migration etc. can lead to such uncertainty.[13] The choice by the FDA to suggest classification cut off limits based on 1 pK_a unit separation to guide the decision of salt vs. co-crystal formation also appears to be somewhat spurious as classically the pK_a separation 'rule of thumb' has been that of a separation of 3 pK_a units will lead to salt formation.[13] Further to this co-crystals have been reported with a pK_a separation of up to 1.5 pK_a units and pK_a has been shown to be a poor indicator of charge state in solids.[14]

Depending on the API in question this guidance could be a further hindrance to market approval as the classification of co-crystals as a formulation additive requires inventors to show the properties of the parent drug. This leads to the potential need to duplicate development effort in novel APIs, especially where the free form presents poor development properties, such as a difficult to crystallise molecule that had only presented in the amorphous form.[15] The need for proof of in-vivo dissociation could also be of significant impact in this regard.

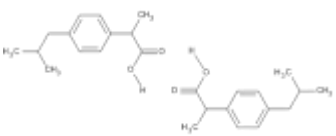
It is therefore envisaged that this guidance will lead to more 'lifecycle management opportunities' and generic applications for co-crystals than for applications for new API molecules to the market.

The regulatory landscape does not detract from the novelty, utility and non-obviousness[16] of these phases however and as such they can still be patented as before. It is not beyond comprehension that the future decisions relating to such patents will be coloured by the FDA guidance, but at present this has not transpired.

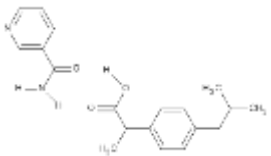
On the whole the authors believe the step by the FDA to release guidance to classify co-crystals has been a positive one; with certain obvious limitations. Evolution is needed in the regulatory definition of hybrid systems, whereby one part of the molecular crystals is a complex and the other is a salt,[17] but previous to this guidance document there was no global regulatory direction readily available. Although there are clear shortcomings in the philosophical stance of the current guidance it does begin to build a regulatory framework in which co-crystals can progress to the market; the absence of which had been an inhibitory factor to co-crystal development. A further potential benefit extending from this guidance is for the regulatory acceptance of co-crystallised excipients (i.e. the converse of API: API co-crystal blends), since co-crystals are simply seen as a formulation. These could beneficially alter the physical properties of excipients which have been safety tested. This potentially represents a new route for 'novel' excipients with differentiated function to be used within the marketplace.

Efficient screening

In order to go through efficient screening there must first be a design strategy. This has largely been focussed on a synthon design approach[18,19] where a homosynthon has been disrupted in preference for a heterosynthon (Figure 1). Historical design strategies have largely focussed on simple molecules with a single homosynthon and as such have not dealt with the competitive interactions within molecules that contain 'self' heterosynthons. The early work on pharmaceutical co-crystals was therefore less immediately applicable in the industrial sector where many molecules followed Lipinski's rules[20] and had multiple donor and acceptor groups.



a) Ibuprofen carboxylic acid homosynthon



b) Ibuprofen: nicotinamide carboxylic acid to amide heterosynthon

Figure 1. Examples of Homo and Heterosynthons

Lipinski's rules were developed to speed up drug design and aid the incorporation of pharmacokinetic considerations into the drug discovery process by rational design. These rules are far from the only measure of 'drug likeness' used in the design of novel drug molecules, but they provide a useful indication of the number of donors and acceptors likely to be found i.e. 5 H-bond donors and 10 H-bond acceptors in a molecule of around 500 Daltons with a LogP of <5. Therefore any screening methods should be able to determine the existence of co-crystals in such molecules.

Screening as an act should allow the efficient removal of irrelevant information to allow concentration of effort on the important, with the minimal loss of useful information in the process. Although distasteful it should be accepted that either a proportion of useless information will be retained from the screening process or useful information will be lost. In a physical form screen the loss of useful information is a greater penalty than retention of useless information. Therefore a multiple step process is preferable to filter out redundancy when dealing with large numbers of compounds, such as will be found in a co-crystal screen. A practically sensible screening paradigm is outlined in Figure 2. As ever the issue of thermodynamically stable and kinetic forms is a dilemma for such screening protocols and needs to be considered. The logic behind this process is based in the early development environment where API material is scarce, typically 500mg-1g of material will be available for a screen. Due to the need to maintain a large chemical library of co-formers if *in-silico* screening is avoided, the process is still applicable when applied to the later stage environment though.

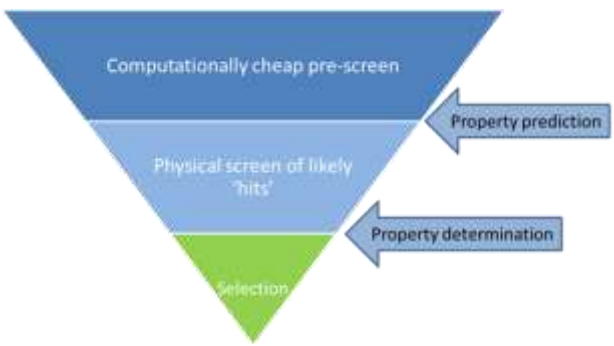


Figure 2. Co-crystal screening protocol

Computationally 'cheap' pre-screen

A number of approaches to deal with computational screening of co-crystals have been used to great success, in terms of both the prediction of the existence and the structure of co-crystals; each has relative drawbacks and advantages. These approaches have varied in methodology from full structure prediction, using anisotropic potentials[21], use of summative surface interactions via electrostatic potential surfaces and COSMO-RS[22] to prediction of the H-bond propensity based on Cambridge Structural Database (CSD) statistics.[23] At the early stage of screening full exploration of the GRAS/EAFUS list requires screening of circa 2000 co-formers with a vast number of conformational permutations and stoichiometric possibilities. It is arguable that it is not appropriate to engage in the level of effort of full structure prediction for all co-crystal: API combinations and their putative stoichiometries at this stage. Therefore at the early stage of screening *in-silico* methods which are computationally cheap, but act as accurate pre-screens are sensible. On a very simplistic level electrostatic potential surface approaches ignore crystal lattice considerations and follow the basic premise that point charges across the surface of the molecule can interact in a pairwise fashion, these will form strongest hydrogen bond donor (HBD) to strongest hydrogen bond acceptor (HBA) interactions as per Etters rules (Figure 3).[24] These rules are then sequentially followed until all interactions across the surfaces are formed. The total energy of the potential solid is then estimated as the sum of all likely contacts. This summative energy is then compared to the sum of self:self interactions for both components. The lower energy, more likely structure, is then ranked against others to predict the most likely co-crystals or lack of them. The computationally intensive element of such an approach is the accurate calculation of the surface. Once the surfaces have been calculated the summative energy calculations can be achieved very swiftly for a number of molecules, conformations and stoichiometries. In future, if computing continues to become cheaper and faster at the current rate, full structure prediction methodologies would be a superior option at this stage.

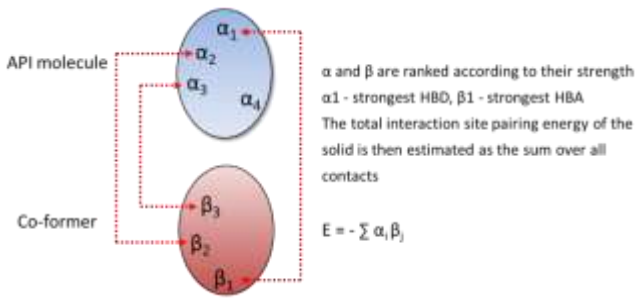


Figure 3. Summative surface energy approach to screening.[22]

Once such approaches have been undertaken a number of the most likely 'hits' can be taken to the physical screening stage directly. A prudent rationalisation should see screening in the region of 50 to 100 systems, but this is obviously dependent on the results of the screen. It is logical to apply further predictive and empirical approaches at this stage of screening to assess the likely applicable functionality of any potential co-crystal selected. Discussion of these approaches will be dealt with in detail in the subsequent discussion of physical properties.

Physical screen of likely 'hits'

A number of excellent reviews and papers have dealt with the processes of physical co-crystal screening.[25] The weight of evidence points to solvent assisted grinding yielding the greatest percentage of co-crystal 'hits' for the number of experiments conducted in the high throughput environment. This is due to the inherent propensity of the technique to function in the region of ternary phase space where co-crystal stability is readily accessible.[26] The reaction crystallisation method[27] also works in this region of phase space with excellent results, but is more complex to conduct practically. The significant benefit of utilising this approach however is

solubility information, which can be used later for crystallisation work, and a greater possibility of single crystal growth; invaluable for property prediction and definition of the phase.

The drawback of solvent assisted grinding is that it is complex to automate in a high throughput fashion i.e. where limited API material is available. This has been somewhat inhibitory to its use as a screening tool on novel APIs, but the use of ultrasound methodologies instead of physical grinding, in a ball mill or with a mortar and pestle etc., has opened the door to automated robotics platforms.[28] This advance has allowed screening in a 96 well plate and, by utilising significantly smaller API quantities, presents another step towards the broader application of pharmaceutical co-crystals. This is because further access to the early development environment will mean that novel APIs can more readily be developed as functional co-crystals. Decisions on form selection are generally made relatively early in the development pathway to allow bulk chemical processes to be appropriately developed and quality assurance to be put in place and validated. By miniaturising screening more co-crystal information can be available at this stage and therefore more co-crystals should be seen in development.

Post determination of the existence of a phase the most efficient means of determining further potential phases (e.g. polymorphs and differing stoichiometric compositions), or lack thereof, within a system is the Kofler melt fusion approach, which has been used to good effect.[29] This obviously requires thermal stability in the materials under investigation.

Property determination

It is widely quoted[30] that 40% of marketed drugs and the majority of development compounds have poor solubility. This is a significant problem for drug development as the ability for the human body to absorb and distribute drugs, steps needed in order for them to exert their action, is based on the aqueous solubility and *in-vivo* permeability of the API. If solubility were the only problem facing drug development then all drug phases should be developed as stabilised amorphous forms, where the solubility advantage is guaranteed and generally in the region of 1-10 times superior.[31] Although this comment is pointedly facetious, due to the innumerate disadvantages of such a strategy, there is some truth in it. Solubility however is not the only problem in drug development. Physical and chemical stability must be sufficient at those temperatures relevant to processing. Flow properties must allow efficient movement of bulk powder in processing. Water must be added in wet granulation processes and tablet compacts must be made. *In-vivo* performance is essential, but a hurdle that must be overcome within the industry is to see co-crystal development as a broader church than simply a route to solubility improvement. Indeed co-crystal solubility can be lower than that of the parent compound.[32] In fact of 80 co-crystal systems analysed, in 20% of cases worse solubility was seen vs. the parent free drug, with one system showing a solubility ratio of >3 times worse. Such is the need for improvements in solubility it cannot be ignored in any drug development strategy however. Therefore co-crystal solubility prediction is essential for removing drug development barriers and allowing the efficient production of function co-crystal material, further study is needed in this area.

Dissolution

One of the earliest signposts that co-crystals would be of interest in drug development was from dissolution data.[2] The spring and parachute model has been discussed widely and is applicable to a number of co-crystal systems. This behaviour is characterised by a transient improvement in concentration and a subsequent drop, normally to the solubility limits of the free form in that pH environment. In some systems the improvement has been seen to be comparable to the amorphous phase, suggesting dissociation, precipitation of amorphous material, then eventual recrystallisation.[2] Dependent on the ternary interactions, on dissolution co-crystal systems have also been seen to retain the drug molecule in the solution state (Figure 4). Here proof of API: co-former dissociation would presumably require greater regulatory scrutiny. The usefulness of either class of behaviour is defined by the timescale and extent of any improvement in concentration, when considered in the context of the intended route of administration. If concentration improvements can be maintained over a bio-relevant timescale then it is strong evidence that a co-crystal phase will possess useful function.

In oral delivery the majority of reproducible drug absorption is from the small intestine where the absorptive surface is large and the pH environment is generally in the region of pH 6.8.[33] Here lies another advantage of co-crystals. In neutral API molecules, where the dissolution behaviour is not driven by pH speciation, one can tailor the release by use of an ionisable co-former.[34] Further to this the use of formulation additives can inhibit free form nucleation after dissociation of the co-crystal, providing a 'parachute' where one does not naturally exist,[35] micellar approaches have also been employed to similar end.[36] These results highlight an area that requires more study in co-crystals and engineering systems which encompass tailored nucleation inhibitors and surfactants as co-formers is an exciting possibility. In such theoretical systems incongruent saturation in the ternary environment would be of benefit, as fast dissociation would lead to a maintained supersaturated state, allowing more drug to be absorbed via the intended route.

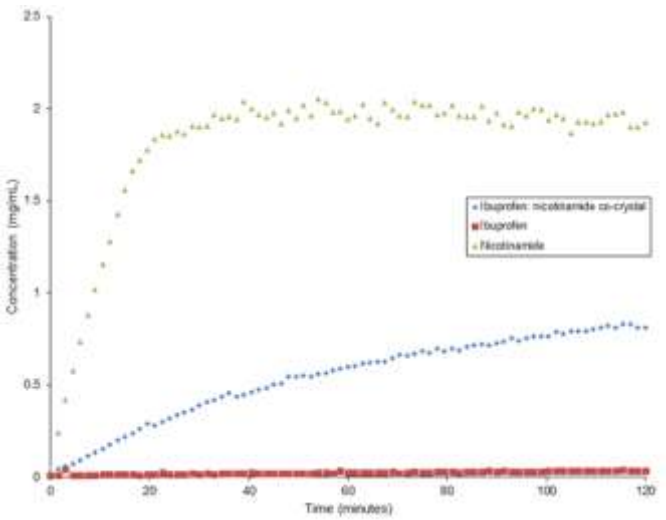


Figure 4. Comparison of dissolution of the individual components and the co-crystal of ibuprofen: nicotinamide. †

The oral drug delivery route represents around 70% of medicines in use, however the dissolution and dissociation

behaviours of co-crystals have so far been poorly explored in non-oral delivery routes. In the instance of ocular and nasal delivery it can be envisaged that there is significant development opportunity based on their dissociation behaviours. Therefore the major hurdle, which must be overcome with respect to dissolution, is the development of co-crystal approaches beyond oral therapy areas, a superior understanding of co-former structure to function relationships and uses in targeted drug delivery approaches.

Resistance to hydration

Although physical and chemical stability on storage is of great utility from the perspective of shelf life, and a primary driver for understanding moisture sorption behaviour, many pharmaceutical processes also require modification of the humidity environment. Indeed processes such as wet granulation often require water to be added directly. This is a significant problem in those systems that are poorly stable to high humidity or disassociate readily.

Early results with caffeine showed that co-crystals could be of benefit here.[6] The moisture sorption behaviour of ibuprofen and nicotinamide has been reported and has been shown to be low.[37] In all cases the figure of <1% moisture uptake would represent low levels of moisture sorption. This behaviour is also replicated in the subsequent co-crystal[37] (Figure 5).

Here co-crystals show a great advantage over salts. The ibuprofen sodium salt, the most widely marketed form, forms a di-hydrate (approximately 13.5% total mass is water) and before formation of this hydrate phase is highly hygroscopic.[38] As such during manufacturing processes the moisture environment must be controlled, this can add significant expense to the development of pharmaceutical phases and be an inhibitory factor to phase development, by increasing drying time etc.

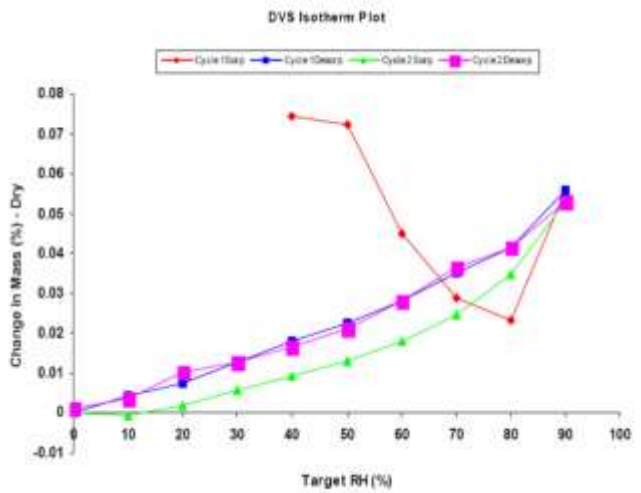
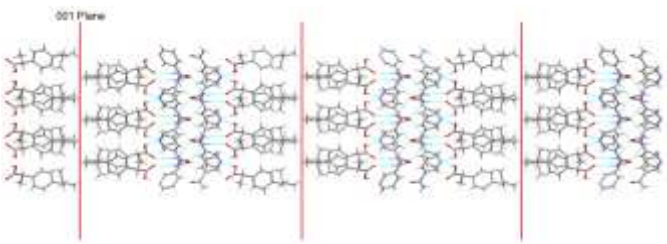


Figure 5. Moisture sorption in the ibuprofen: nicotinamide co-crystal system.† Loss of moisture in the first cycle is attributed to a proportion of amorphous content produced from grinding.

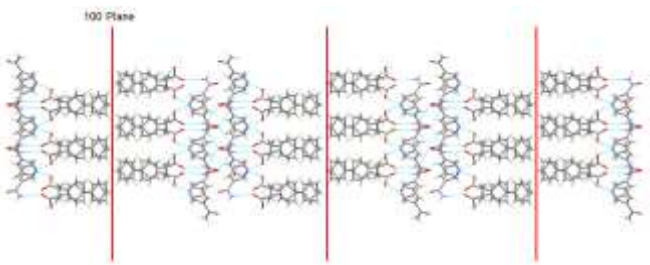
A high degree of moisture absorption is a property, which also leads to stickiness and poor powder flow. This is another property that co-crystals have been seen to improve.[39] This very simple property can have a large impact on the production of all solid dosage forms, for example tablets and capsules. Knowledge of structure/function correlation between co-fomer and co-crystal would be a significant advantage in this area too.

Compaction behaviours

The tableting behaviour of an API can be altered by formulation approaches, but if high drug loading is needed, in order to produce once a day formulations for example, the tableting behaviour of the drug phase becomes increasingly important. Co-crystallisation has been shown to both improve and worsen tableting performance.[6,39] These behaviours have been rationalised by the crystal structure of the co-crystal vs. the parent drug. In the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen and flurbiprofen improvements in tableting performance vs. the parent were seen when co-crystallised with nicotinamide.[37] Tablet strength, i.e. the tensile strength of the compressed powder, is gained from interactions between particles of a given material. Bonding area between particles dictates this strength and it has been established that plastic deformation of particles, along with size reduction by brittle fracture, is critical in the formation of a large bonding area by compaction.[40] Slip planes within structures mean that they have lower yield strength, are more plastic and therefore form stronger more dense compacts. Such slip planes can be seen in the crystal structures of both the ibuprofen and flurbiprofen co-crystals (Figure 6).



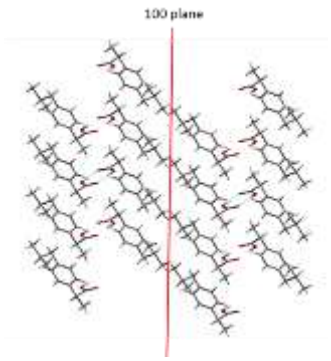
a) R/S Ibuprofen: nicotinamide co-crystal viewed down the a-axis.



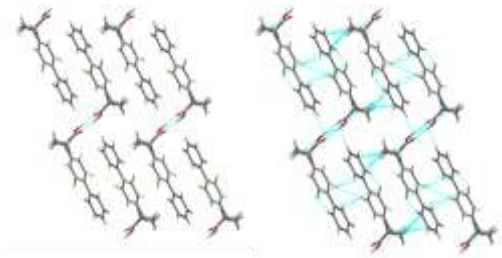
b) R/S flurbiprofen: nicotinamide co-crystal† viewed down the c-axis.

Figure 6. Slip planes in the R/S ibuprofen (a) and R/S flurbiprofen (b) : nicotinamide co-crystal structures. Slip planes are highlighted in red.

Both structures display clear planes along which limited bonding can be seen; both in terms of H-bonding and weaker bonding forces. Thus reducing the yield strength of the materials and improving compaction behaviours. Of the two parent molecules R/S ibuprofen showed significantly superior tableting performance, again slip planes are clearly evident in the structure, this is not the case in the stable polymorph of flurbiprofen (see Figure 7) where offset π-π stacking allows bonding in all planes.



a) RS Ibuprofen (IBPRAC) viewed down the b-axis. The slip plane is highlighted in red.



b) RS flurbiprofen (FLUBIP01) viewed down the a-axis. Left image is without Van der Waals interactions shown, right image with.

Figure 7. Crystal structures of ibuprofen (IBPRAC) (a) and flurbiprofen (b)

It should be noted that, a crystal structure of nicotinamide with naproxen, another non-steroidal anti-inflammatory drug (NSAID), has been identified (PAMQAX). Sadly no tablet formation or compression data is available for this phase. This co-crystals structure possesses comparable H-bond motifs and slip planes to the API: nicotinamide co-crystals displayed here. Therefore, although potentially biased by the small size of the dataset, improved tableting behaviour can been seen across a series of similar drug molecules when using the same co-former (nicotinamide). Nicotinamide possesses good tableting properties and is a brittle material.[37] Not all co-formers are the as useful in this arena and broader consideration of the property which is required from a co-crystal is always recommended.

If similar results are borne out in larger datasets physical property prediction of co-crystals will become more feasible across homologous series. This is potentially very important when considering the way in which drug development and discovery activities are usually conducted i.e. with a target based focus. These results show that there is potential for a reduction of screening effort across a set of discovery compounds and realisation of preferred co-formers for particular purposes, if adequate structure property relationships can be identified.

Crystallisation and scale up

Efficient production approaches are essential if co-crystals are to become more widely utilised. Classic solution crystallisation approaches are the most industrially applicable due to the habitual use of such technology across the globe and indeed have been used to good effect.[15] Within this conventional approach the issues imposed by the phase diagram[41] for the chosen solvent: co-fomer: API ternary system, need careful consideration; from initial solid form isolation through to scale up activities. The impact of solvent choice on the isolated stochiometric composition, in relation to solution stoichiometric composition,[42] has significant implications. Solubility differences of 2 times would mean that half of the more soluble component would always be lost to the solvent. This could obviously be recovered, but at a cost. This highlights again the importance of advances in solubility prediction.[32] Solubility product (SP) models have been applied to systems under specific conditions with a great deal of success, but further investigation into self-seeding phenomena[43] and continued development of solubility models, to address the working limitations of SP models, is needed. These points require further work in order to draw a line on the debate to use the solution crystallisation route. Consequently, either proceeding on this route or making significant moves away from such technology, although possible, will represent the need for significant investment across the industry and academia; especially if continuous processes are to be considered.

Solvent crystallisation methods have been utilised to produce co-crystals from a thermal inject printer.[45] Such technology could have many exciting applications in the production of multiple drug tablet platforms or to produce tailored modified release systems based on a patients phenotypical variance; the latter could be achieved by utilising mixtures of the free drug and one or more co-crystals. It is suggested by the authors of this work that this technology could be used for early development screening too.

Other techniques have been used for the production of co-crystals and would be compatible with continuous processing strategies. Extrusion represents the most studied bulk process for co-crystal manufacture and significant advances have been made using IR as a process analytical tool (PAT).[46] Freeze drying is another technology that has been shown to readily apply to co-crystallisation.[47] Like co-grinding the co-crystal product is produced by transfer through an amorphous phase. This highlights the need for adequate understanding of crystallisation kinetics in co-crystal systems, regardless of the route of production. Supercritical fluid technology and gas anti-solvent methods have been used to good effect.[48] Microwave synthesis has also been used for the production of co-crystals.[49] Microwave synthesis failed to produce changes, from the starting components to co-crystal material, in the caffeine: maleic acid system without solvent, the technology has shown excellent promise as a continuous manufacturing technology with the aid of solvent however.

Conclusions

Although there is a weight of evidence, which continues to build, for the use of pharmaceutical co-crystals they still represent a greater cost and perceived risk to development than a comparable salt. The future is bright though and in instances where no salt can be made, or where those explored are unsuitable, co-crystals present a very real and viable option for development. As screening and selection strategies should encompass the breadth of solid forms and soft matter with time even in instances where a salt is possible co-crystals may well be selected; once structure to function relationships have been thoroughly explored. Moves away from arguments based simply on oral delivery and GI dissolution behaviour are needed along with computational screening approaches to utilise the full gamut of co-crystal possibility. Robust analysis of co-crystal: API: co-former structure property relationships, and dissociation behaviours, are also required to optimise screening and manufacturing efficiency. Once these have been investigated functional co-crystal material should be more readily accessible as a realistic option to deliver medicines to patients and improve lives.

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Experimental†

Dissolution

Dissolution was performed using the rotating disc method, and run at 37°C in 500mL of phosphate buffer at pH 7; which mimics the pH environment of the lower intestine. The discs were made from compacts of 150mg of pure component or co-crystal, which were compressed at a pressure of 1 metric tonne for 1 minute. *In-situ* UV probes were used to measure the concentration within the solution media (in an N = 2 study). These probes were calibrated with 1mg/mL aqueous methanol solutions of the respective solids. The dissolution concentration was then calibrated against the λmax of the various adducts (260nm ibuprofen, 276nm nicotinamide) allowing good mapping of concentration against time.

Dynamic Vapour Sorption

DVS was performed using the surface Measurement Systems (SMS) Advantage dynamic vapour sorption (DVS) instrument utilising a set of sorption, desorption cycles on 10.65mg of sample in 10% humidity steps. Samples were weighed until of consistent mass at a given humidity.

Crystal growth

Single crystals were grown from a seeded mixture of flurbiprofen (R/S) (0.614 mmol) and nicotinamide (3.7 mmol) in 500 μL of ethanol, temperature cycled utilising a Grant LTC 6-30 water bath. The sample was sequentially cooled and heated in a saw-toothed cycle from 288K to 283K over 50 hrs.

Crystallography†

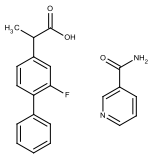

Figure 8. Flurbiprofen and nicotinamide

$C_{21}H_{20}FN_2O_3$, $M = 367.39$, Monoclinic, $P2_1/c$, $a = 27.459(1)$ Å, $b = 5.6654(2)$ Å, $c = 11.4275(5)$ Å, $\beta = 92.250(2)^\circ$, $\alpha = \gamma = 90^\circ$, $V = 1776.4(1)$ Å^3, $T = 120(2)$ K, $Z = 4$, μ (Mo K$_\alpha$) = 0.100 mm^{-1}, 17171 reflections measured, 3958 unique ($R_{int} = 0.0651$) which were used in all calculations. The final wR_2 was 0.1448 (all data) and R_1 was 0.0543 ($I \geq 2\sigma(I)$).

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